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10/505,268	08/20/2004	George A Doherty	21045P	5437

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EXAMINER	
CHUNG, SUSANNAH LEE	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/505,268	DOHERTY ET AL.	
	Examiner	Art Unit	
	Susannah Chung	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/7/04; 10/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are currently pending in the instant application and are subject to the following new lack of unity requirement.

Election/Restrictions

Restriction is required under 35 U.S.C. 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

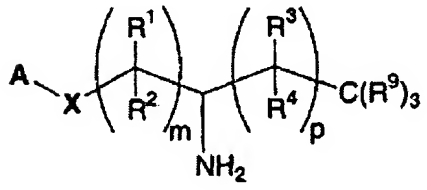
Claims 1-20 are drawn to more than one inventive concept (as defined in PCT Rule 13), and accordingly, a restriction is required according to the provision of PCT Rule 13.2

PCT Rule 13.2 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a general inventive concept (requirement of unity of invention).

PCT Rule 13.2 states that unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features.

Due to the numerous and widely divergent variables in the compound of formula (I), for example A, X, R1, R2, m, R3, R4, p, R9, etc., a precise listing of inventive groups cannot be made. The following groups are exemplary:

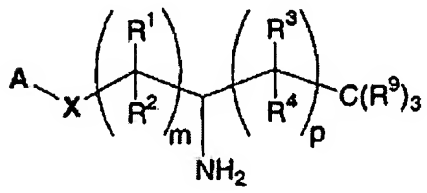
Group I: Claims 1, 2 and 4-20 drawn to compounds of formula (II),



, wherein A is PO3H2; X is a bond; R1, R2, R3, R4, and R9

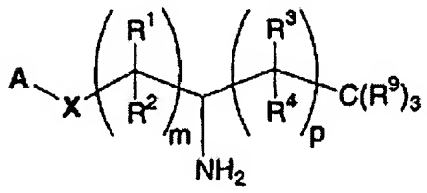
are hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

Group II: Claims 1-20 drawn to compounds of formula (II),



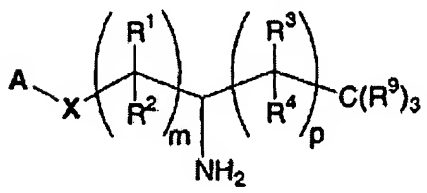
, wherein A is PO3H2; X is O; R1, R2, R3, R4, and R9 are hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is bone marrow rejection.

Group III: Claims 1-20 drawn to compounds of formula (II),



, wherein A is PO3H2; X is O; R1, R2, R3, R4, and R9 are hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is graft-versus-host disease.

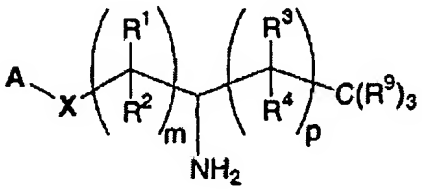
Group IV: Claims 1-20 drawn to compounds of formula (II),



, wherein A is –CO2H; X is O; R1, R2, R3, R4, and R9 are

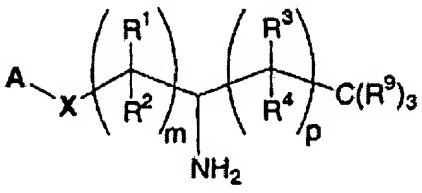
hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

Group V: Claims 1-20 drawn to compounds of formula (II),



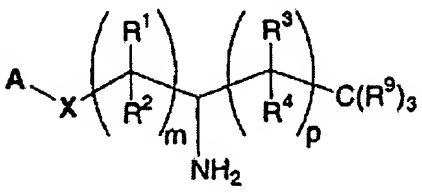
, wherein A is –SO3H; X is O; R1, R2, R3, R4, and R9 are hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

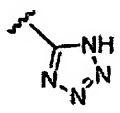
Group VI: Claims 1-20 drawn to compounds of formula (II),



, wherein A is –PO(R8)OH; X is O; R1, R2, R3, R4, and R9 are hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

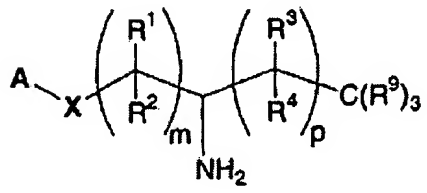
Group VII: Claims 1-20 drawn to compounds of formula (II),

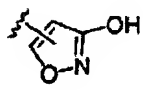


, wherein A is  ; X is O; R1, R2, R3, R4, and R9 are

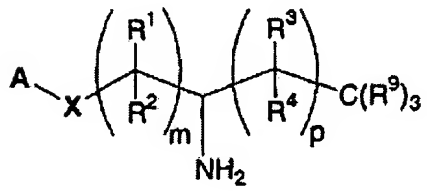
hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

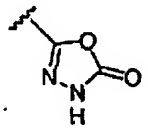
Group VIII: Claims 1-20 drawn to compounds of formula (II),



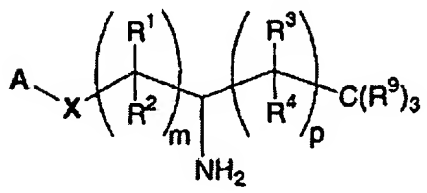
, wherein A is  ; X is O; R1, R2, R3, R4, and R9 are hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

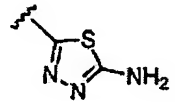
Group IX: Claims 1-20 drawn to compounds of formula (II),



, wherein A is  ; X is O; R1, R2, R3, R4, and R9 are hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

Group X: Claims 1-20 drawn to compounds of formula (II),



, wherein A is  ; X is O; R1, R2, R3, R4, and R9

are hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

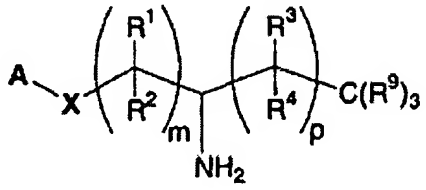
In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Again, this list is not exhaustive as it would be impossible under the time constraints due to the sheer volume of subject matter instantly claimed. Therefore, applicant may choose to elect a single invention (in this case a product, Compound B, or a method of making a product, Compound A) by identifying another specific embodiment, i.e. another value for A, X, R1, R2, m, R3, R4, p, R9, etc..., not listed in the exemplary groups of the invention and examiner will endeavor to group the same.

The claims herein lack unity of invention under PCT rule 13.1 and 13.2 since, under 37 CFR 1.475(a) the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art. The technical feature of the instant claim(s) is the amine, which does not define a contribution over the prior art. The variables off the amine vary from compound to compound in the instant claims and when taken as a whole result in vastly different compounds.

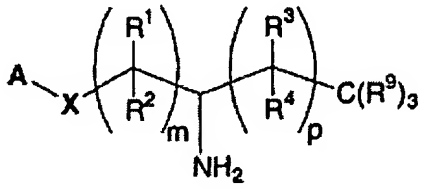
Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper. Additionally, the vastness of the claimed subject matter, and the complications in understanding the claimed subject matter imposes a serious burden on any examination of the claimed subject matter.

During a telephone conversation with Attorney Raynard Yuro, on 30 August 2006 a provisional election was made *with traverse* to prosecute the invention of Group I, comprising

Claims 1-20 drawn to compounds of formula (II),  , wherein A is PO3H2; X is a bond; R1, R2, R3, R4, and R9 are hydrogen; m is 1 and p is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection. Affirmation of this election must be made by applicant in replying to this Office action.

Scope of the Elected Invention

Claims 1-20 are pending in this application. The scope of the elected subject matter that will be examined and searched is as follows:

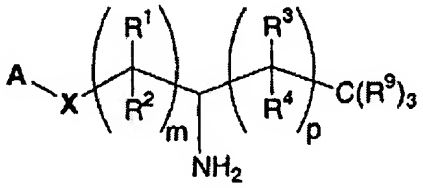
Compounds of Formula (II),  , depicted in claim 1, page 68, wherein:

A is PO3H2; **X** is a bond; **R1**, **R2**, **R3**, **R4**, and **R9** are hydrogen; **m** is 1 and **p** is 9, and methods of using the compound of formula (II) to treat an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

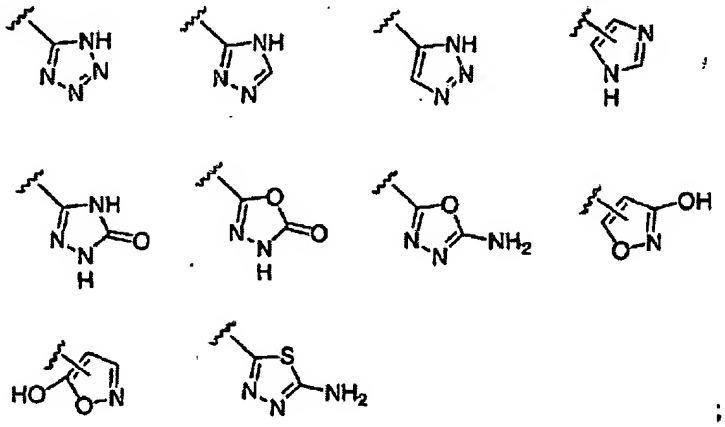
Scope of Withdrawn Subject Matter

Claims 1 (in part), 2 (in part), 3 and 4-20 (in part) are withdrawn from further consideration by the examiner, 37 C.F.R. §1.142(b), as being drawn to a non-elected invention. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in structure and element and would require separate search considerations. In addition, a reference, which anticipates one group, would not render obvious the other.

The scope of the withdrawn subject matter that will not be examined and searched is as follows:

Compounds of Formula (II),  , depicted in claim 1, page 68, wherein:

A is CO2H, PO2H2, SO3H, PO(R8)OH,



X is O, NH, S(O)k; and methods of using the compound of formula (II) to treat anything other than an immunoregulatory abnormality, wherein the immunoregulatory abnormality is organ transplant rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

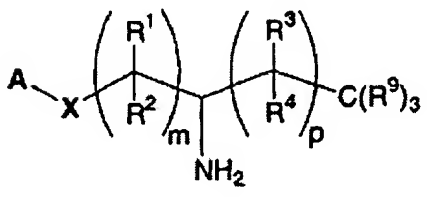
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al., U.S. Pat. No. 6,670,399.

Applicants instant elected invention teaches the compound of formula (II),



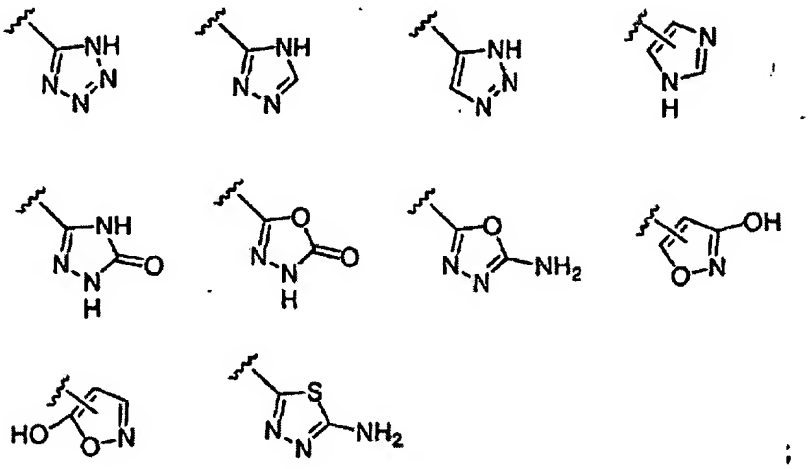
, depicted in claim 1, wherein:

m = 1, 2, 3, or 4;

p = 9 to 20;

X is a bond, O, NH, $S(O)_k$, wherein k is 0, 1 or 2;

A is selected from the group consisting of: $-CO_2H$, $-PO_3H_2$, $-PO_2H_2$, $-SO_3H$, $-PO(R^8)OH$,



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Determination of the scope and content of the prior art (MPEP § 2141.01)

Green teaches phosphonate compounds and salts of formula H2PO3-alkyl chain substituted by an amine and Na2PO3-alkyl chain substituted by an amine. The preferred embodiments include a straight chain alkyl with 30 or fewer carbons atoms in its backbone. (See US Pat. 6,670,399, column 17, lines 61-63). Green teaches the following exemplary compounds: 3-Aminopropylphosphonic acid,(1-Aminopropyl)phosphonopropanoic acid; (dl)-3-Amino-butylphophonic acid; (dl)-3-Amino-pentylphosphonic acid; (dl)-3-Amino-hexylphosphonic acid; (dl)-3-Amino-heptylphosphonic acid; (dl)-3-Amino-octylphosphonic acid (CAS RN 373644-73-

6); (dl)-3-Amino-4-methyl-pentylphosphonic acid; 3-Amino-3-methyl-butylphosphonic acid, etc... (see US Pat. No. 6,670,399, columns 25-28, and 37-40).

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the prior art of Green and the instant claims is that in the prior art the length of the alkyl chain differs. The length of the alkyl chain is longer in the instant application , i.e. wherein p is 9 to 20.

Finding of prima facie obviousness – rationale and motivation (MPEP § 2142-2413)

However, in the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with Green to make products useful to treat immunoregulatory disorders, wherein 3-aminooctyl-phosphonic acid is 3-aminotridecylphosphonic acid.

Guided by the teaching of Green one skilled in the art would be able to make similar compounds by varying the length of the alkyl chain. The motivation would be to prepare similar compounds that are pharmacologically active. The prior art of Green teaches the use of the instant compounds to prevent the cell death, especially in blood vessels. The instant application claims the use of the compounds in the treatment of immunoregulatory abnormalities, which could include death to blood vessel cells causing disease in a mammal.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The biological data provided in the specification on pages 57-67 do not enable one of ordinary skill in the art to practice this invention.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claims 7-13 of the present invention below:

(1) The Nature of the Invention

Claims 7-19 are directed to methods of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound in accordance with Claim 1 in an amount that is effective for treating said immunoregulatory abnormality.

(2) The Breadth of the claims

Claims 7-19 will be give its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, Claims 7 and 19, which do not specify the many possible disorders that would be classified as an immunoregulatory abnormality will be interpreted to encompass all disorders. Claims 8-17 will be interpreted to encompass the broadest definition of the disorders claimed.

(3) The state of the prior art

The state of the art at the time of this application was that the phosphonic acid compounds of the instant application are known to treat cerebral amyloid angiopathy, which is a pathological condition of small cerebral vessels characterized by deposits of amyloid in the vessel walls, which may lead to infarcts or hemorrhage. (See US Pat. No. 6,670,399, column 1). In addition, phosphonic acids are known to inhibit squalene synthetase and are ultimately useful to treat hypercholesterolemia and atherosclerosis (US Pat. No. 5,428,028, column 1).

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether the instantly claimed compounds although known to treat cerebral amyloid angiopathy, hypercholesterolemia, and atherosclerosis could be reliably and predictably extrapolated to in vivo activity in patients with other immunoregulatory abnormalities. There is no absolute predictability, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The instant specification discloses biological data to support the use of the instantly claimed compounds in the treatment of immunoregulatory abnormalities, but does not explain how and which diseases it targets in particular.

(7) The presence or absence of working examples

The specification may disclose general biological data to support the use of this compound in the treatment of certain diseases, but the specification presents no working examples and one skilled in the art would not know which diseases the compound of the instant application would be most effective.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of the compounds of formula (II), it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients with which diseases would benefit from which of the many claimed compounds within the scope of the invention with a reasonable expectation of success.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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